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Frequency of cervical hpv in women with COVID-19 infection

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Abstract
Aim: At the beginning of 2020, the Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus emerged in China. While there are several studies currently being performed to investigate the multi-organ symptoms of COVID-19 infection, significant attention has yet to be paid to its presence in the cervix. This article aims to establish a medical hypothesis of its association with HPV infection as well as the potential impact of COVID-19 infection on the female genital tract.
Material and Methods: This prospective cohort study was performed in ... Research and Training Hospital between January 1 and July 30, 2020. Cervicovaginal samples (co-test) were taken at the gynecological oncology unit, and both HPV screening and Pap smear were studied with the liquid-based method. Two groups of patients who were confirmed by PCR test to have had COVID-19 infection in the last 6 months and patients who did not have a history of infection were included in the study.
Results: A total of 310 participants were evaluated in the study. Of these participants, 30 (9.7%) were confirmed to have undergone COVID-19 by PCR test. There was no significant difference between the total positive smear results in both groups. However, the rate of HPV-16 positive patients was significantly higher in the COVID-19 group (2.5% vs 10.0%, p=0.027).
Discussion: As a result, COVID-19 infection may increase the frequency of HPV-16. Apart from this, it can be said that this increase is not reflected in the frequency of cervical cytopathology.

Keywords
Cervical Cancer Screening, Co-Test, Coronavirus, COVID-19, HPV, SARS-CoV-2

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Introduction

Viral diseases constitute serious public health problems all over the world. In the last eighteen years, worldwide viral outbreaks have been reported, such as the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002 and the Middle East Respiratory Syndrome Coronavirus (MERSCoV) in 2012. At the beginning of 2020, the SARS-CoV-2 virus and the Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 emerged in China. This clinical condition was officially reported by the World Health Organization on the last day of 2019. However, it was understood that traces of a viral infection were present as of November 2019 and were defined as "pneumonia of unknown etiology" [1, 2]. Although governments around the world have implemented many precautions, the number of cases has increased day by day. Health organizations are coordinating data and issuing recommendations and guidelines to reduce and eliminate the effects of the pandemic worldwide. However, there is still much research to be done on the precise etiopathogenetic mechanisms and the many complications caused by COVID-19 infection.

Although the virus is caught through the upper respiratory tract and causes serious illness in the lower respiratory tract, there is evidence to support its effects on many organs and systems. Differently from the respiratory system, it has been shown that SARS-CoV-2 genetic material is detected in blood and plasma samples and spreads to the hematological system [3, 4]. It has been shown to spread throughout the body by this way and has effects on the kidneys, liver, heart, brain and gastrointestinal system [5-10].

The relationship between COVID-19 infection and the female genital system has not yet been clearly demonstrated. However, some indications are present. In a study investigating the presence of COVID-19 in semen and conducted among 38 men, the presence of SARS-CoV-2 was shown in 15.8% of them [11, 12]. Although the percentage is not relatively high and the physiology of the male reproductive system is different from that of women, a virus predominantly found in the respiratory system appears to affect semen. Therefore, the possibility of its presence in the cervical tissue seems plausible.

HPV creates unique effects on the cervical epithelium, unlike other parts of the female genital tract. The first of these is the trigger effect that may be on carcinogenesis. The cervix is the most clearly known part of the female genital tract system affected by the virus [13].

While there are several studies currently being performed to investigate the multi-organ symptoms of COVID-19 infection, significant attention has yet to be paid to its presence in the cervix. There is a study conducted on 35 patients by Cui et al. In this study, the presence of SARS-CoV-2 in the genital tract was not demonstrated in any of the patients diagnosed with COVID-19. However, this study is dated March 2020. However, after this date, the epidemic spread all over the world, but observational studies involving more patients on this subject have not been published. Except for the presence of this virus in the genital tract of patients with active COVID-19 infection, there has been no literature study on the presence of HPV and subtype analysis in women who have had this infection. HPV genetically has little in common with coronaviruses, but may have common features in terms of transmission process or lifecycle. Moreover, the rate of HPV infection in the cervical epithelium of women with COVID-19 infection and women who do not have this infection is unknown. This may be important given the immunosuppressive effect of HPV. Studies examining the detection of genetic material of SARS-CoV-2 in cervical cytology samples are insufficient. In this study, the frequency of infection with HPV within the scope of the cervical screening program in women who had COVID-19 infection compared to women who did not have this infection, and if related, which subtypes were observed and cervical cytopathological changes were investigated. In case of positivity of one of the high-risk HPV types, patients underwent colposcopy and the results of this pathology were compared among the patient groups. This article aims to establish a medical hypothesis of its association with HPV infection as well as the potential impact of COVID-19 infection on the female genital tract.

Material and Methods

This prospective cohort study was performed in ... Research and Training Hospital between January 1 and July 30, 2020. The study protocol was approved by our Ethics Committee (Ethics Committee number 2020-13). The study represents a subgroup of sample collected from patients who applied to our center for co-testing (HPV test with cervicovaginal smear application) within the scope of the routine cervical cancer screening program of the Ministry of Health of the Republic of Turkey. Cervicovaginal samples (co-test) were taken at the Van Research and Training Hospital gynecological oncology unit, and both HPV screening and Pap smear were studied with the liquid-based method. Smear results and HPV results were evaluated by the gynecological oncology unit. In our study, all patients with high-risk HPV positivity underwent colposcopy by the same gynecologist oncologist. During colposcopy, 3% acetic acid was used and an average of 2 cervical biopsies were taken. Each patient was informed before the procedure. After the cervix was treated with 3% acetic acid, the transformation zone was examined with a colposcope. A Tischler punch biopsy sample was taken from abnormally observed areas (such as acetowhite area, coarse punctuation area, mosaic pattern, etc.) and sent to the laboratory on the same day.

Two groups of patients who had confirmed COVID-19 infection by PCR test within the last 6 months and patients who did not have a history of infection were included in the study. Informed consent was obtained from all participants before the study commenced. Women aged 18-65 years, without HPV DNA positivity in cervicovaginal smear examination, without cervical cancer and cervical preinvasive lesion history, who did not receive HPV vaccine and who did not have immunodeficiency were included in the study. Grand multiparous patients were excluded from the study. In the study, the group with COVID-19 infection was made up of women who did not have active COVID-19 infections, who had fully recovered and had completed the quarantine period. Patients who met the inclusion criteria during the study period and patients who agreed to participate in the study were consecutively included in the study.

HPV positivity and HPV subtype were determined by co-test for both groups. In addition, those with negative smear results,

Atypical Squamous Cells of Undetermined Significance (ASCUS), Low-Grade Intraepithelial Lesion (LSIL), High-Grade Squamous Intraepithelial Lesion (HSIL) and Atypical Squamous Cells-Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) were reported. Colposcopy results were divided into 4 groups as Normal/chronic cervicitis, Cervical Intraepithelial Neoplasia (CIN1), Cervical Intraepithelial Neoplasia (CIN2), and Cervical Intraepithelial Neoplasia (CIN 3).

Statistical analysis

All data collected for statistical analysis were analyzed with the Statistical Package for the Social Sciences, version 23, SPSS Inc., Chicago, IL (SPSS). Age was given as mean ± standard deviation, median (minimum, maximum), while categorical variables were given as numbers (%). When comparing the age variable that matches the normal distribution with the Student T-test, the Chi-square test was used to evaluate the categorical data. The statistical significance level was taken below 0.05.

Results

A total of 310 participants were evaluated in the study. Smoking and the number of pregnancies showed a homogeneous distribution among the groups. Of these participants, 30 (9.7%) were confirmed to have undergone COVID-19 by PCR test. In the control group, there were 280 (90.3%) participants without a history of COVID-19. Age values of the groups showed homogeneous distribution (p=0.363). There was no significant difference between the total positive smear results of both groups.

However, the rate of HPV-16 positive patients was significantly higher in the COVID-19 group (2.5% vs 10.0%, p=0.027). There was no significant difference between the groups in the positivity rates of HPV-18 and other HPV types (Table 1). Colposcopy was performed on all patients with positive high-risk HPV. In the comparison of the pathologies of the groups after colposcopy, no significant difference was found between chronic cervicitis, CIN1, CIN2 and CIN3 (p=0.564) (Table 2).

Table 1. Comparison of age groups with HPV results

	Control group (n=280)	COVID-19 group (n=30)	P value
Age	43.7±8.7	46.2 ± 14.3	0.363
Smear			
Positive	29 (10.6)	4 (13.3)	0.615
Negative	251 (89.6)	26 (86.7)	
HPV 16			
Positive	7 (2.5)	3 (10.0)	0.027
Negative	273 (97.5)	27 (90.0)	
HPV 18			
Positive	5 (1.8)	0 (0.0)	0.461
Negative	275 (98.2)	30 (100.0)	
HPV (other)			
Pozitive	35 (12.5)	3 (10.0)	0.692
Negative	245 (87.5)	27 (90.0)	

HPV, Human papillomavirus. Continuously variable data are shown as mean ± standard deviation, median (minimum, maximum), categorical variables are presented as numbers (percentage). Significant p values are displayed in bold.

Table 2. Comparison of cervical pathologies of the groups

	Control group (n=280)	COVID-19 group (n=30)	P value
Normal / Chronic Cervicitis	238 (85)	24 (80)	0.564
CIN1	18 (6.4)	3 (10.0)	
CIN2	2 (0.7)	1 (3.3)	
CIN3	6 (2.1)	1 (3.3)	
Chronic Cervicitis	16 (5.7)	1 (3.3)	

CIN, Cervical intraepithelial neoplasia. Variables are presented in numbers (percentage).

Discussion

As the virus continues to spread worldwide, it is important to understand the consequences of SARS-CoV-2 infection. SARS-CoV-2 has been previously detected in the throat, anal swabs, urine and tears [12]. However, few reports have been submitted on the isolation of the SARS-CoV-2 virus directly in the female genital tract [14]. In these reports, it was emphasized that the virus could be detected in cervicovaginal secretions and therefore the necessary precautions should be taken in the gynecological examination. It is also suggested that an ulcerated lesion in the vulva and the isolation of SARS-CoV-2 RNA from this lesion may cause ulcerative lesions in the genital tract. It is clear that there is strong evidence pointing to multi-organ involvement of COVID-19. Since its effect has been shown for multiple organs, it would be reasonable to assume its potential effect on the female genital system as well. Although it has not been shown to be found directly in the cervical epithelium, its isolation in the cervicovaginal secretion may be an indirect indicator of this condition. In addition, although it has not been shown to cause a direct lesion in the cervix, the isolation of SARS-CoV-2 RNA in an ulcerated lesion in the vulva suggests that it may potentially cause a macroscopic or microscopic lesion in the cervix [14].

On the other hand, HPV can be considered the most common sexually transmitted infection in terms of prevalence in the general population [15]. Both heterosexual and homosexual HPV transmission is possible through penetrating and even non-penetrating sexual contact. Most infected men and women do not show clinically significant signs or symptoms [16]. The reported frequencies of low- and high-risk HPV subtypes are similar for women. Skin or mucosal microlesions allow infection of normal cells in the basal epithelial layer with HPV.

SARS-CoV-2 isolation from the cervix during the COVID-19 infection has not yet been performed. However, the potential for SARS-CoV-2 to infect the cervical epithelium may also increase the risk of HPV infection. The increase in co-test HPV positivity in patients with COVID-19 infection may confirm this situation. However, in this study, the frequency of positive HPV was not different in women who had COVID-19 infection compared to women who did not. On the other hand, when HPV subtype analysis was performed, the frequency of HPV-16 was found to be significantly higher in women who had COVID-19 before. This shows that the frequency of cervical HPV-16 positivity in a woman who has had a previous COVID-19 infection is increased compared to other HPV subtypes.

However, in order to be able to link this situation to the previous COVID-19 infection, there is a need to define the physiopathological mechanisms that can explain the increase in the frequency of cervical infection with HPV in patients with COVID-19 infection. A prospective observational study on the detection rates of SARS-CoV-2 genetic material in cervical

cytology is also ongoing [17]. Clinical cervical specimens from this study will be immersed in a bottle containing collection fluid (Hologic). The cytological material will then be analyzed for the presence of COVID-19 genetic material by storing the cells for a long time and, in the case of positive results, HPV typing will also be performed to detect potential correlations between SARS-CoV-2 infection and HPV infection.

With a study of this design, it may be possible to confirm the increased frequency of HPV-16 that we found in patients with COVID-19 infection. In addition, there have been observations that patients with known HPV infection later infected with COVID-19 may cause progression in cervical pathology [17]. The progression of known HPV positivity to CIN 1 lesion on colposcopy after COVID-19 infection for a patient without cervical lesion has led to the observation that there may be a correlation between HPV and COVID-19 infection. However, case-based observations are not sufficient to confirm this hypothesis. These observations need to be confirmed by randomized or cohort studies. Potentially, the mechanism of this situation may not be related to SARS-CoV-2 infection itself, but to impaired immune system, which is already considered a known factor for the occurrence of cervical pathology.

However, our study does not provide information to explain this situation. Because this study was conducted between 2 groups of women who did not have a history of HPV before. For this reason, it does not have a design to explain the progression of the current HPV infection in cervical pathology. The general methodology of the study is that the effect of having a COVID-19 infection on the immune system makes it predispose to HPV infection and if it does, which types cause an increase in frequency.

If, as in this study, COVID-19 infection causes an increase in HPV-16 prevalence, it would not be an exaggeration to conclude that patients exposed to SARS-CoV-2 virus should be followed up more regularly to optimize early detection of cervical premalignant lesions. This may be due not only to the general effects that COVID-19 may have on the female immune system, but also to some unknown interactions between the two viruses.

Our study has some shortcomings. In our study, the number of patients who had COVID-19 was less than the control group. In addition, COVID-19 is an infection that can be transmitted asymptomatically, and the history of COVID-19 infection was only verbally questioned, and serological confirmation was not provided that this infection was not experienced before. This can be a confounding factor. The potential correlation between COVID-19 infection and HPV infection can be demonstrated by planning randomized studies with larger numbers of patients in which confounding factors are eliminated. Due to the limited number of cases, this study is insufficient to strongly demonstrate this relationship.

On the other hand, this study is the first in the literature to identify a correlation between the two viruses in terms of the unknown effects of SARS-CoV-2 on the genital tract. This may encourage other researchers to increase their interest in demonstrating the relationship between HPV and SARS-CoV-2.

Conclusion

COVID-19 infection may increase the frequency of HPV-16. Apart from this, it can be said that this increase is not reflected in the frequency of cervical cytopathology. However, it is highly probable that this is due to the short-term nature of the study. Again, the COVID history does not seem to be a factor affecting the colposcopy results in our study. The colposcopy results of patients with and without COVID-positive HPV can be evaluated according to their HPV types, and the number of patients and groups can be compared, but this is the subject of another study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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